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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/032,221	12/21/2001	Raghuram Kalluri	2312/2082B	3472

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 05/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/032,221	KALLURI, RAGHURAM	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 November 2004 and 04 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-107* is/are pending in the application.

4a) Of the above claim(s) *43-50,52,53 and 55-107* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-42,51 and 52* is/are rejected.

7)☒ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 11/08/04 and 3/04/05, is acknowledged.

2. Claims 1-107 are pending.

3. Claims 43-50, 52, 53 and 55-107 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

4. Claims 1-42, 51 and 52 are under consideration in the instant application as they read on an isolated fragmetn of SEQ ID NO: 10 and SEQ ID NO: 37-42 as the species.

5. The following new ground of rejection is necessitated by the amendment submitted 3/4/04.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 3-42, 51 and 52 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The phrase "comprising amino acid residues 77-95 of SEQ ID NO: 10" claimed in claims 1, 6, 15, 20, 29 and 34 represents a departure from the specification and the claims as originally filed.

Applicant's amendment filed 3/4/04 does not point to the specification for support for the newly added limitations "comprising amino acid residues 77-95 of SEQ ID NO: 10" as claimed in claims 1, 6, 15, 20, 29 and 34. However, the specification does not provide a clear support for such limitation. The instant claims now recite a limitation, which was not clearly disclosed in the specification and recited in the claims as originally filed.

8. In view of the amendment filed on 11/08/04, only the following rejections are remained.

9. Claims 2, 6-9, 20-23 and 34-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated fragment of SEQ ID NO: 37, having the ability to inhibit tumor growth, inhibit angiogenesis and inhibit protein synthesis in endothelial cells, SEQ ID NO: 38 having the ability to inhibit protein synthesis in endothelial cells, and SEQ ID NO: 39-42 having the ability to inhibit tumor growth, does not reasonably provide **enablement** for an isolated mutated fragment comprising amino acid residues 77-95 of SEQ ID

NO: 10, wherein one or more, and five or fewer, amino acids have been substituted, and wherein the mutated fragment has the ability to inhibit tumor growth in claim 6 or inhibt angiogenic activity in claim 20 or inhibit protein synthesis in claim 34, wherein the mutated fragment is reduced in claims 7, 21, 35, wherein the fragment is alkylated in claims 8, 22 and 36, wherein the fragment is oxidized in claims 8, 22 and 37, or an isolated polypeptide "having" the amino acid sequence of SEQ ID NO: 37 in claim 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim for the same reasons set forth in the previous Office Action mailed 5/5/04.

The term "having" in claim 2 is open-ended, it would open the 25 amino acids of SEQ ID NO: 37 to include additional unspecified amino acids on either or both sides of the N-termini or C-termini.

Applicant's arguments, filed 3/04/05 and 11/8/04, have been fully considered, but have not been found convincing.

Applicant submits that they are not "relaying upon certain biological activities and the disclosure of a single species to support an entire genus.". Nor do the claims encompass a broad genus of fragments with an unlimited number of possibilities with regard to the length of the polypeptide sequence." Rather each of the amended claims recite Tumstatin fragments comprising a defined amino acid sequence. Applicant submits that the specification describes the formula for producing a generic active peptide based on the Tumstatin sequence. Applicant submits that 36 polypeptides are not a "myriad," but rather is a reasonable number of species based on the exemplary mutant polypeptides shown to retain tumor inhibitory activity.

However, the claims 6, 20 and 34 recite "one or more, and five or fewer amino acids" substitutions of SEQ ID NO: 10 that provides up to (5X19) 95 substitutions (for naturally occurring amino acids), not all which are necessarily predictive of inhibiting tumor growth, angiogenic activity, or protein synthesis in endothelial cells. Therefore, absent the ability to predict which of these polypeptides would function as claimed for one of skill in the art to practice the invention as claimed would require a level of experimentation that is excessive and undue.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1-2, 6, 15, 20, 29, 34, 51 and 54 are rejected under 35 U.S.C. 102(b) as being anticipated by Kalluri *et al* (J Biol. Chem. 271:9062-9068, 1996) (IDS Ref. No. 45), as is evidenced by the provisional application 60/126,175 on page 26.

Kalluri *et al* teach a deletion of 26 amino acids in the triple helix and NC1 region (α3/n-26) fragment of the wild type α3(IV) chain. Kalluri *et al* further teach a deletion of N-terminal triple helix 26 aa and C- terminal 36 amino acid (α3/n-26/c-36). Kalluri *et al* further teach mutated fragment, α3/n-26/c-KK having a deletion of N-terminal triple helix 26 aa and substitution of last two lysines to alanines (see the entire document and page 9064 under Figure 1 in particular). While the prior art teachings may be silent as to the ability to "inhibit tumor growth", "inhibit angiogenic activity","inhibit protein synthesis in endothelial cells", the protein synthesis is " cap-dependent protein synthesis" and the endothelia cells "express the αvβ3 integrin" per se; the product in Kalluri *et al* reference is the same as the claimed product. Therefore "inhibit tumor growth", "inhibit angiogenic activity", and "inhibit protein synthesis in endothelial cells" is considered inherent properties. Further, as is evidenced by the provisional application 60/126,175 on page 26, under example 1 that the referenced fragment of NC1 domain (N-terminal deletion) have anti-tumor and angiogenesis activity.

When a claim recites using an old composition or structure (e.g. fragment of SEQ ID NO: 10) and the use is directed to a result or property of that composition or structure (inhibiting tumor growth, angiogenesis and protein synthesis in endothelial cells), then the claim is anticipated. See MPEP 2112.02. Also, see Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc. 58 USPQ2d 1508 (CA FC 2001); Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

The reference teachings anticipate the claimed invention.

Applicant's arguments, filed 3/04/05 and 11/8/04, have been fully considered, but have not been found convincing.

Applicant argues that the claims recite the active site sequence of amino acids 77-95. Applicant concludes that the claimed fragments are distinguished from the truncated Tumstatin and synthetic polypeptides disclosed in Kalluri et al and Monbosse et al., respectively.

Contrary to applicant conclusion the Kalluri et al truncated fragments comprise the amino acids 77-95 of SEQ ID NO: 10. Specially, because the truncation of the 26 amino acids occurs at the N-terminal of the α3 chain. The amino acids 77-95 is intact in the truncated fragments.

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject

matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1, 3, 6-7, 15, 17, 20-21, 29, 31 and 34-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kalluri *et al* (J Biol. Chem. 271:9062-9068, 1996) (IDS Ref. No. 45) in view of U.S. Patent 5,858,670.

The teachings of Kalluri et al references have been discussed, supra

The claimed invention differs from the reference teachings only by the recitation that the fragment is reduced.

The `670 patent teaches that a reduced peptide bond may be introduced as a dipeptide subunit. Such a molecule would be resistant to peptide bond hydrolysis, e.g., protease activity. (Col., 10 lines 50-61 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce the fragments taught by Kalluri et al as reduced fragment as taught by `670 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because such reduced fragments would be resistant to peptide bond hydrolysis as taught by the `670 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. Claims 1, 4, 6, 8, 15, 18, 20, 22, 29, 32, 34 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kalluri *et al* (J Biol. Chem. 271:9062-9068, 1996) (IDS Ref. No. 45 in view of U.S. Patent 5,326,875.

The teachings of Kalluri et al reference have been discussed, supra

The claimed invention differs from the reference teachings only by the recitation that the fragment is alkylated.

The `875 patent teaches that alkylated peptides can be purified by crystallization or by silica gel chromatography. Further the `875 patent teaches that proteced alkylated peptides are readily soluble in acidic aqueous medium (Col., 3 lines 43-68 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce the fragments taught by Kalluri et al as alkylated fragment as taught by `875 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because such alkylated fragments are readily soluble in acidic aqueous medium as taught by the `670 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

15. Claims 1, 5, 6, 9, 15, 19-20, 23, 29, 33-34 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kalluri *et al* (J Biol. Chem. 271:9062-9068, 1996) (IDS Ref. No. 45) in view of U.S. Patent 5807,821.

The teachings of Kalluri et al reference have been discussed, supra

The claimed invention differs from the reference teachings only by the recitation that the fragment is oxidized.

The `821 patent teaches that a variety of protecting groups can be incorporated into the synthesis of linear peptide to facilitate isolation, purification, and/or yield of the desired peptide. Protection of cysteine residues found in the peptide can be accomplished using, for example, a triphenylmethyl, acetamidomethyl and/or 4-methoxybenzyl group in any combination. Such a strategy may offer advantages for subsequent oxidation studies to yield folded peptide. (Col., 8 lines 45-60 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce the fragments taught by Kalluri et al as oxidized fragment as taught by `821 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because such oxidation of the peptide offer advantages for subsequent oxidation studies to yield folded peptide as taught by the `821 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments, filed 3/04/05 and 11/8/04, have been fully considered, but have not been found convincing.

Applicant argues that the claims now recite the active site sequence of amino acids 77-95. Applicant concluded that the truncated Tumstatin of Kalluri et al is now distinguished from the prior art.

Contrary to applicant conclusion the prior art of Kalluri's truncated fragments still reads on the claimed fragments of α3 chain comprise the amino acids 77-95 of SEQ ID NO: 10. Because the truncation of the 26 amino acids occurs at the N-terminal of the α3 chain and the aa 77-95 are not affected by said deletion. The amino acids 77-95 is intact in the truncated fragments.

16. No claim is allowed.

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be

obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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May 24, 2005

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